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| 09/966,847 | 09/28/2001 | Rina Goldshtein | 23908-501 | 5004 |
| 30623 | 7590 | 06/25/2004 | EXAMINER | |
| MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C. ONE FINANCIAL CENTER BOSTON, MA 02111 | | | LEWIS, PATRICK T | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1623 | |

DATE MAILED: 06/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/966,847

Applicant(s)

GOLDSHTEIN, RINA

Examiner

Patrick T. Lewis

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 April 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 and 33-53 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-18 and 33-53 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 1-18 and 33-49) wherein the lipophilic compound/particle is a vitamin, antibiotic or hormone and wherein the amphiphilic polymer is a natural polysaccharide in Paper No. 8 dated April 11, 2003 is acknowledged.

Applicant's Response dated April 15, 2004

2. In the Response filed April 15, 2004, claims 1, 8, 33, and 43 were amended; claims 50-53 were added.

3. Claims 1-18 and 33-53 are pending. An action on the merits of claims 1-18 and 33-53 is contained herein below.

4. The provisional double patenting rejection of claims 5, 8-10, 12-18, 43-44, and 46-49 under 35 U.S.C. 101 has been rendered moot in view of applicant's amendment dated April 15, 2004.

5. The rejection of claims 1-7 under 35 U.S.C. 102(e) as being anticipated by Parikh et al. US 6,228,399 (Parikh) has been rendered moot in view of applicant's amendment dated April 15, 2004.

6. Applicant's arguments with respect to claims 8-18 and 33-49 under 35 U.S.C. 103(a) have been considered but are moot in view of the new ground(s) of rejection.

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Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-7 and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Liversidge et al. US 5,145,684 (Liversidge).

Liversidge discloses dispersable particles consisting essentially of a drug substance having a surface modifier absorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 400 nm (Abstract). Suitable drug substances include antibiotics and hormones (column 3, line 53 to column 4, line 5). Suitable surface modifiers include carboxymethylcellulose, methylcellulose, hydroxyethylcellulose, and hydroxypropylcellulose (column 4, lines 34-54). Liversidge further discloses that effective average particle size of less than about 100 nm has been achieved (column 5, lines 30-32).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which

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said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 8-18, 33-49 and 51-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rolfes et al. U.S. Patent 6,221,399 (Rolfes) in combination with Parikh et al. U.S. Patent 6,228,399 (Parikh) and Liversidge et al. US 5,145,684 (Liversidge).

Claims 8-18 33-49 and 51-53 are drawn to a method for forming a hydrophilic inclusion complex comprising forming an emulsion comprising an amphiphilic molecule in an aqueous solvent and lipophilic compounds in a non-aqueous solution, forming nano-sized lipophilic particles in a nano-emulsion, and removing carrier solvent from nano-emulsion. Applicant has elected to have the invention examined wherein the lipophilic particles are vitamins, antibiotics, or hormones and wherein the amphiphilic polymer is a natural polysaccharide.

Rolfes teaches process for making a controlled release product for oral administration from an interpolymer complex and an active agent (column 4, lines 39-67; column 5, lines 1-18). The process comprises: 1) dissolving a first polymer in a solvent therefor, 2) dissolving a second complementary polymer in a

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solvent therefor, 3) mixing the first polymer solution and the second complementary polymer solution, 4) mixing the combined polymer solution of step 3 with the active agent in the form of a dry powder or in the form of a solution, dispersion, suspension, emulsion or slurry of the active agent in a liquid medium, and 5) spraying the product of step 4 into a vessel to remove at least partially the solvents and thereby to produce solid particles of the interpolymer complex. The solvents and liquid medium used may be the same or different (column 9, lines 17-37). Rolfes teaches the use of vitamins and antibiotics as active agents incorporated into the interpolymer complex (column 8, lines 1-4). Polymers used to form the interpolymer complex include guar gum, cellulose and its derivatives, starches and their derivatives, and xanthan gum (column 8, lines 32-64). The complexation occurs via reversible physical molecular forces such as hydrogen bonding, hydrophobic interactions, van der Waals forces, electrostatic- ionic- or Coulomb forces and combinations of these interactions excludes irreversible chemical forces such as covalent bonding (column 6, lines 46-51).

Rolfes differs from the instantly claimed invention in that: 1) Rolfes does not teach active agents as nano-sized; 2) Rolfes does not explicitly teach dissolving the active agent in a non-aqueous solvent; 3) Rolfes teaches the use of two polymers; and 4) Rolfes does not describe the apparatus employed in forming the inclusion complex; however, these deficiencies would have been obvious to one of ordinary skill in the art at the time of the invention when viewed in light of Parikh and Liversidge.

Parikh teaches compositions of sub-micron and micron stable particles of water-insoluble or poorly soluble drugs or other industrially useful insoluble compounds (column 1, lines 5-18). The compositions contain microparticles consisting essentially of a drug, a phospholipid, and at least one surface modifier (Abstract). The term "micro" refers to a particle having diameter of from nanometers to micrometers (column 1, lines 32-46). The surface modifiers/phospholipids generally adsorb to surfaces of drug particles, and convert lipophilic to hydrophilic surfaces with increased stability and possibly modify the zeta potential of surfaces with more charge repulsion stabilization (column 2, lines 20-40). Phospholipid and surface modifier(s) are adsorbed onto the surfaces of drug particles in sufficient quantity to retard drug particle growth, reduce drug average particle size from 5 to 100 μm to sub-micron and micron size particles by one or combination of methods known in the art, such as sonication, homogenization, milling, microfluidization, precipitation or recrystallization or precipitation from supercritical fluid, and maintain sub-micron and micron size particles on subsequent storage as suspensions or solid dosage form. The formulations may be dried, e.g., by lyophilization, fluid or spray drying, into powders, which can be resuspended or filled into capsules or converted into granules or tablets with the addition of binders and other excipients known in the art. Examples of preferred water-insoluble drugs include immunosuppressive agents such as cyclosporins, antibiotics, sedatives, hormones, and nutrients (column 2, lines 59-67; column 3, lines 1-46). The phospholipid may be any natural or synthetic phospholipid. Examples of suitable surface modifiers include

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methylcellulose, hydroxycellulose, hydroxypropylcellulose, polyethylene glycols, and chitosans. Formulations containing microparticles provide some specific advantages over the unformulated non-micronized drug particles (column 1, lines 32-47). The advantages include improved oral bioavailability of drugs that are poorly absorbed from GI tract, development of injectable formulations that are currently available only in oral dosage form, less toxic injectable formulations that are currently prepared with organic solvents, sustained release of intramuscular injectable drugs that are currently administered through daily injection or constant infusion, and preparation of inhaled, ophthalmic formulation of drugs that otherwise could not be formulated for nasal or ocular use.

Liversidge teaches dispersable particles consisting essentially of a drug substance having a surface modifier absorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 400 nm (Abstract). Suitable drug substances include antibiotics and hormones (column 3, line 53 to column 4, line 5). Suitable surface modifiers include carboxymethylcellulose, methylcellulose, hydroxyethylcellulose, and hydroxypropylcellulose (column 4, lines 34-54). Liversidge further teaches that effective average particle size of less than about 100 nm has been achieved (column 5, lines 30-32). The particles are prepared in a method comprising the steps of dispersing a drug substance in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the drug substance to an effective average particle size of less than about 400 nm (column 5, line 40 to column 7, line 9). The particles can be reduced in size

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in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

It would have been obvious to one of ordinary skill in the art at the time of the invention utilize nano-sized active agents to form the inclusion complex taught by Rolfes and Liversidge. One of ordinary skill in the art would have been motivated to employ formulations of nano-sized particles based on the disclosure of Parikh which teaches specific advantages over the unformulated non-micronized drug particles. One of ordinary skill in the art is seen as one having a PhD in organic chemistry or biochemistry conducting research in the field of host-guest chemistry. It would have also been obvious to one of ordinary skill in the art at the time of the invention use a single amphiphilic polymer such as hydroxypropylcellulose to form the instantly claimed complex as taught by Liversidge. Although not specifically taught by Rolfes, it would have been obvious to one of ordinary skill in the art to use a non-aqueous solvent to dissolve drugs that are not water-soluble. The employment of appropriate experimental conditions such as temperature, solvent selection, and drying method are seen to be well within the purview of one of ordinary skill in the art. Although Rolfes does not describe the apparatus for forming the polymer inclusion complex in great detail, Rolfes teaches that the polymer solution and the active agent solution are prepared separately and then mixed. In the absence of some proof of a secondary nature to obviate the instant rejection, or of some specific limitations which would tip the scale of patentability in the favor of the instantly claimed invention, it would have been obvious to one of ordinary

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skill in this art at the time of the invention to formulate a hydrophilic inclusion complex comprising forming an emulsion comprising an amphiphilic molecule in an aqueous solvent and lipophilic compounds in a non-aqueous solution, forming nano-sized lipophilic particles in a nano-emulsion, and removing carrier solvent from nano-emulsion.

Conclusion

12. Claims 1-18 and 33-53 are pending. Claims 1-18 and 33-53 are rejected. No claims are allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on M-F 10:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick T. Lewis, PhD
Examiner
Art Unit 1623



Dr. Samuel Barts
Primary Patent Examiner
Technology Center 1600

ptl
June 23, 2004